The Oncologist®

Radiation Oncology

Nutrient Restriction and Radiation Therapy for Cancer Treatment: When Less Is More

COLIN E. CHAMP,[a] RENATO BASERGA,[b] MARK V. MISHRA,[a] LIANJIN JIN,[a] FEDERICA SOTGIA,[b] MICHAEL P. LISANTI,[b] RICHARD G. PESTELL,[b] ADAM P. DICKER,[a] NICOLE L. SIMONE[a]

[a]Department of Radiation Oncology, Kimmel Cancer Center, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA; [b]Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Calorie restriction • Intermittent fasting • Radiotherapy • Cancer

CME Learning Objectives

Identify molecular pathways that are potential targets of calorie restriction combined with radiation therapy.

Identify cancer patients for whom calorie restriction would be contraindicated.

Abstract

Calorie restriction (CR), or a diet modification aiming to reduce the total intake of calories by 20%–40%, has been shown to increase longevity across multiple species. Recently, there has been growing interest in investigating the potential role of CR as a treatment intervention for age-related diseases, such as cancer, because an increasing body of literature has demonstrated a metabolic component to both carcinogenesis and tumor progression. In fact, many of the molecular pathways that are altered with CR are also known to be altered in cancer. Therefore, manipulation of these pathways using CR can render cancer cells, and most notably breast cancer cells, more susceptible to standard cytotoxic treatment with radiation and chemotherapy. In this review article we demonstrate the laboratory and clinical evidence that exists for CR and show compelling evidence through the molecular pathways CR induces about how it may be used as a treatment in tandem with radiation therapy to improve our rates of disease control. ***The Oncologist*** 2013;18:97–103

Implications for Practice: Dietary manipulation via caloric restriction (CR) has been shown to decrease the incidence of cancer and enhance cancer treatment. CR affects several molecular pathways, such as the insulin and AMP-kinase pathway, which are also known to enhance the effectiveness of radiation therapy in preclinical studies. These pathways are a source of interest, as they are targeted by several current anticancer agents currently being used in clinical trials. Therefore, CR may provide a cost-effective addition to current treatment modalities that enhances cancer therapy while minimizing side effects, and may improve metabolic profiles during survivorship. CR may be unsuitable for some cancer patients, but it has been shown to decrease treatment side effects, and may be efficacious in cancer subtypes whose outcomes appear to correlate with metabolic status, such as breast cancer. Since CR may provide a therapeutic intervention that enhances current standard cancer therapy such as radiation, and decreases treatment toxicity, clinical trials are now warranted.

Introduction

Calorie restriction (CR) is, to date, the only modality proven to increase longevity across multiple species. Recently, there has been growing interest in investigating the role of nutrient deprivation as a treatment intervention for age-related diseases, including cardiovascular disease, diabetes, ocular disease, and cancer [1]. Evidence suggests a metabolic component to cancer that would make CR an attractive therapy to be combined with conventional treatment, such as radiation therapy (RT).

CR is a diet modification that aims to reduce total caloric intake to a level 20%–40% lower than that of a typical diet, without limiting essential vitamins and nutrients [2]. CR can be achieved through overall dietary reduction (DR) or by intermittent fasting (IF) [3]. CR has been further shown to induce changes in molecular pathways, many of which are also altered in cancer, making CR an attractive modality to explore. Altering these pathways can leave cells more susceptible to treatment with RT. The primary objective of this article is to review the laboratory and clinical evidence supporting the role of CR as a novel cancer treatment intervention that may be used as an adjunct to traditional treatment approaches such as RT to improve disease control.

Correspondence: Nicole Simone, M.D., Department of Radiation Oncology, Thomas Jefferson University, Kimmel Cancer Center, Bodine Center for Cancer Treatment, 111 S. 11th Street, G-301G, Philadelphia, Pennsylvania 19107, USA. Telephone: 215-503-0554; Fax: 215-955-0412; e-mail: nicole.simone@jeffersonhospital.org Received April 11, 2012; accepted for publication September 24, 2012; first published online in ***The Oncologist*** *Express* on January 8, 2013. 1083-7159/2013/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0164

CME

Laboratory and Clinical Evidence

Over a century of in vivo laboratory research has demonstrated the utility of CR in the oncologic setting [1]. In 1909, Moreschi demonstrated that transplanted sarcoma tumors in mice fed a CR diet prior to the transplantation had significantly slower growth than those fed an ad libitum (AL) diet [3]. A year later, Rous initiated CR after tumor induction and confirmed Moreschi's results showing lower rates of spontaneous tumor development, metastasis, and tumor recurrence [4, 5]. Tannenbaum furthered the field by applying strict food measurement techniques to evaluate the extent of CR and showed that carbohydrates may be the important macronutrient to restrict [6]. These findings have been confirmed in the last three decades, demonstrating 1.7- to 44-fold lower spontaneous tumor growth in CR-fed mice [6, 7] than in AL-fed animals [2]. These studies demonstrate the ability of CR to slow tumor growth by 50%–80% [3, 8–10]. Perhaps most importantly, CR has also been shown to lead to longer survival times after cancer induction [11, 12]. Recent studies have revealed slower breast cancer growth, angiogenesis, and metastasis [9].

Human data have paralleled animal studies, suggesting a benefit of CR for cancer treatment [12–14]. Multiple population-based studies of underweight patients have revealed a significantly lower cancer incidence than in the general population. Data from Swedish patient registries have shown a lower risk for breast cancer in patients with anorexia nervosa [15] and a similar Danish registry revealed a lower overall cancer risk [16]. A lower cancer-related death rate was also seen in populations who have overall lower calorie consumption. This has been shown in gastric bypass surgery patients, who often reduce their caloric intake >50% (with patients consuming as low as 820 kcal/day 18 months after surgery) and experience a significantly lower incidence of cancer and lower cancer mortality rate [17–20]. A study comparing cancer rates in people from mainland Japan with those of residents of Okinawa, where significantly fewer calories are consumed, found the Okinawa population to have lower cancer rates and cancer mortality rates [21]. It is unknown, however, if these effects were related to CR or the adoption of a more westernized diet in mainland Japan.

Conversely, it is known that obesity can lead to a higher risk for developing cancer [22, 23], and prospective studies have demonstrated an association between obesity and cancer-specific mortality in multiple sites [23]. Biologically, obesity is associated with high levels of circulating insulin, lower insulin sensitivity, and insulin resistance [24]. Additionally, breast cancer patients often undergo a period of less physical activity and greater weight gain during treatment and subsequently present with an unfavorable metabolic profile following chemotherapy [25]. Weight gain after a breast cancer diagnosis is associated with poor outcomes [26], and CR has been shown to lower body weight and increase fat loss. Consequentially, the antitumorigenic effects of CR seem to be particularly relevant to our breast cancer population during treatment and survivorship.

The relationship among insulin metabolism, obesity, exercise, and cancer has led to a recent surge of interest in dietary intervention during cancer treatment. This is exemplified with newer trials, such as the National Cancer Institute of Canada MA.32 trial, which is treating early-stage breast cancer patients with standard therapy and randomizes them to placebo or metformin, which affects several metabolic pathways.

Molecular Evidence Connecting CR and RT

The ability of CR to slow tumor growth is likely attributable to the induction of several molecular changes (Table 1). CR increases apoptosis while augmenting antiproliferative effects and decreasing DNA synthesis [27, 28]. It is hypothesized that this reduction in cell proliferation is a major effect by which CR decreases tumor growth [29, 30]. In fact, many novel therapeutic agents for cancer treatment are targeted against molecules known to also be targets of CR, such as insulin grown factor-1 receptor (IGF1-R), the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). Therefore, CR may be a novel anticancer intervention given that many molecular targets can be altered simultaneously. Furthermore, evidence in humans suggests that CR via IF may potentiate the antitumor effects of chemotherapy while protecting normal cells, resulting in lower rates of treatment-related side effects [31].

IGF Pathway

The IGF-1R pathway plays a role in the pathogenesis of breast cancer, and higher expression levels are associated with poor outcomes [32–35]. IGF-1, a circulating growth factor that modulates cell proliferation by binding to IGF-1R, protects cells from apoptosis, increasing cancer risk through activation of insulin receptor substrate (IRS) and PI3K [32, 36]. The activation of these pathways and inhibition of apoptosis have led to the proposition that IGF-1R and the glucose pathway should be considered targets for cancer treatment. Further, it has been noted that IGF-1 is decreased in response to CR [33].

Breast tumors often express higher IGF-1 and IGF-1R levels than normal breast tissue [37–40]. Overexpression of IGF-1 is associated with aggressive breast cancer phenotypes, such as triple-negative breast cancer [41, 42]. IGF-1 and IGF-1R have also been correlated with earlier recurrence and resistance of breast cancer to chemotherapy and RT as well as a shorter relapse-free survival interval in human studies [43, 44]. Data from other cancer sites has shown IGF-1 to decrease effectiveness of RT, which is reversed when IGF-1R is blocked [45].

DR can reduce serum IGF-1 concentration by up to 40% [1]. In a breast cancer mouse model, a CR diet decreased both IGF-1R expression and serum insulin levels [46]. Human data are lacking, but studies of female adolescents suffering from anorexia reveal lower levels of IGF-1 [47].

Cytotoxic cancer treatments such as RT and chemotherapy decrease IGF and IGF-1R levels (Fig. 1). Conversely, IGF-1 has been shown to inhibit apoptosis induced by tamoxifen and 5-fluorouracil, decreasing their efficacy in human breast cancer cells in a mouse model [48]. RT causes upregulation of IGF-1R within as little as 10 minutes of treatment [49], likely as a survival mechanism for cancer cells after radiation-induced damage. Inhibiting IGF-1R can increase the radiosensitivity of breast cancer cells and the potential therapeutic efficacy of RT against these cells [43]. The same study revealed higher early breast cancer relapse rates within 4 years of treatment in patients whose tumor specimens showed overexpression of IGF-1R. Inhibition of IGF-1R in human breast cancer cells leads to induced apoptosis, inhibited proliferation, and enhanced ra-

Table 1. Biologic factors affected by CR

Mitigated by CR	Increased by CR
Obesity	Apoptosis
Insulin resistance	Decreased DNA synthesis
IGF-1	Antiproliferation
IGF1-R	Tumor growth inhibition
Elevated blood glucose	LKB1
AKT	AMPK
PI3K	Cost-effectiveness
Angiogenesis	Metabolic profile
mTOR	

Abbreviations: AMPK, AMP-activated protein kinase; CR, calorie restriction; IGF-1, insulin like growth factor 1; IGF1-R, IGF-1 receptor; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

diosensitivity [50]. Fasting results in a 75% decrease in IGF-1 after 2–5 days [51, 52], while chronic DR results in only a 23% reduction [53].

Taken together, these data suggest that reduction of IGF-1 and IGF-1R may increase tumor cell kill with RT, and this can potentially be achieved through CR diet modification using an approach that is targeted to tumor cells.

IRS, PI3K, AKT

Both IRS-1 and PI3K have also been shown to be overexpressed in breast cancer [54, 55]. IRS-1 and IRS-2 activate PI3K following IGF-1 binding to its receptor [56]. AKT is then directly affected by PI3K further downstream.

CR decreases IRS-1 and PI3K [57], resulting in greater radiosensitivity and significant tumor regrowth delay, both in vivo and in vitro [58–62]. AKT potently increases radioresistance by providing irradiated cells the ability to overcome radiation-induced apoptosis and bypass the p53-independent G_2-M cell-cycle checkpoint [58]. Like PI3K, AKT is also reduced by CR in mammary tumors [63]. Interestingly, disruption of IGF-1R and the downstream PI3K and AKT pathways by nutrient deprivation and stress also increased longevity in experiments with *C. elegans* by inducing dauer [64]. Thus, CR-induced reduction in both PI3K and AKT may be another mechanism through which CR potentiates the antitumor effects of RT.

mTOR: The Pathway Connecting IGF and AMPK

mTOR is one of the most commonly altered cellular pathways in tumors [65]. mTOR, which is activated by PI3K, regulates cell growth via nutrient import, cell survival, protein translation, and decreased autophagy [66]. Studies suggest that the mTOR inhibitor rapamycin partially mimics the effects of CR by inhibiting activation of AKT and mTOR and simultaneously decreasing circulating IGF-I [67, 68]. Inhibition of mTOR pathways by upstream inhibition through CR and downregulation of mTOR protein production may also lead to radiosensitization of cancer cells, but this has not yet been studied in detail.

AMPK

mTOR is also inhibited by the AMPK pathway. This recently received much attention in the oncology community because of pilot trials using metformin, which activates this pathway [56]. *AMPK*, a tumor suppressor gene [69], serves as a functional sensor of cellular energy status and regulates metabolism by impeding cell growth, proliferation, and metabolic signaling. It inactivates synthesis of fatty acids and cholesterol [70] and directly and indirectly inhibits mTOR [71], resulting in greater mitochondrial activity [72, 73]. During times of stress, mTOR engages AMPK to promote catabolic cell behavior while decreasing the anabolic pathways of protein and fatty acid synthesis [70].

In this manner, AMPK is activated by CR and other low energy conditions, leading to cell autophagy and mitophagy [69, 70]. CR may therefore reduce the ability of cancer cells to repair damage and continue metabolism for cell survival. Metformin mimics CR by lowering circulating insulin, increasing insulin sensitivity, decreasing circulating IGF-1, and decreasing the IGF-1R pathway [74].

AMPK is activated by RT in breast cancer cells and potentially radiosensitizes cancer cells [75]. Although the mechanism of radiosensitization is unclear [71, 75, 76], loss of AMPK results in inactivated radiation-induced G_1/S checkpoints [72] and G_2/M arrest [75]. Metformin allows for AMPK to regain its activity, leading to shorter survival times of breast cancer cells [77]. The loss of metabolic control after RT likely results in a lower rate of cell proliferation, defective checkpoints, and ultimately greater cell kill.

Metformin has been shown to decrease the incidence of breast cancer and mortality rate of breast cancer patients and is currently being assessed in several phase II and phase III trials [56, 78]. This combined metabolic advantage and direct manipulation of cancer pathways, such as mTOR, PI3K, and AKT, further exemplify the potential benefits of CR (Table 2). CR can theoretically inhibit several critical pathways in the development and progression of cancer, while simultaneously rendering malignancies more sensitive to treatments such as chemotherapy and RT.

Clinical Trials

CR, especially via fasting, is an attractive adjunctive treatment for cancer because it is a lifestyle intervention that may provide patients with a better metabolic profile. While long-term DR may result in chronic weight loss, IF prior to and after each RT treatment may be a potential method to induce CR and inactivate molecular pathways of radioresistance while avoiding significant weight loss.

To date, CR has been successfully implemented alone in several human trials dealing with metabolic disorders. CR studies from the 1950s by Ancel Keys are often referenced; however, these studies employed extreme dietary modifications whereas current CR studies have evolved to become more tolerable for patients [79]. More recently, several CR studies have been undertaken to evaluate the feasibility and efficacy of CR and the metabolic changes induced in patients. CR regimens vary widely across these trials, and although some are extreme, for example, allowing patients only 400 calories per day for 2 months [80], most employ regimens that would be more easily tolerated during a course of RT and in normal life. Also, IF may be a method to further increase adherence while mitigating weight loss and potential side effects.

Methods of measuring adherence to a diet modification such as CR remain difficult in an outpatient setting. To date, dietary trials for diseases such as diabetes have relied on food journals and questionnaires. Methods of increasing adher-

CME

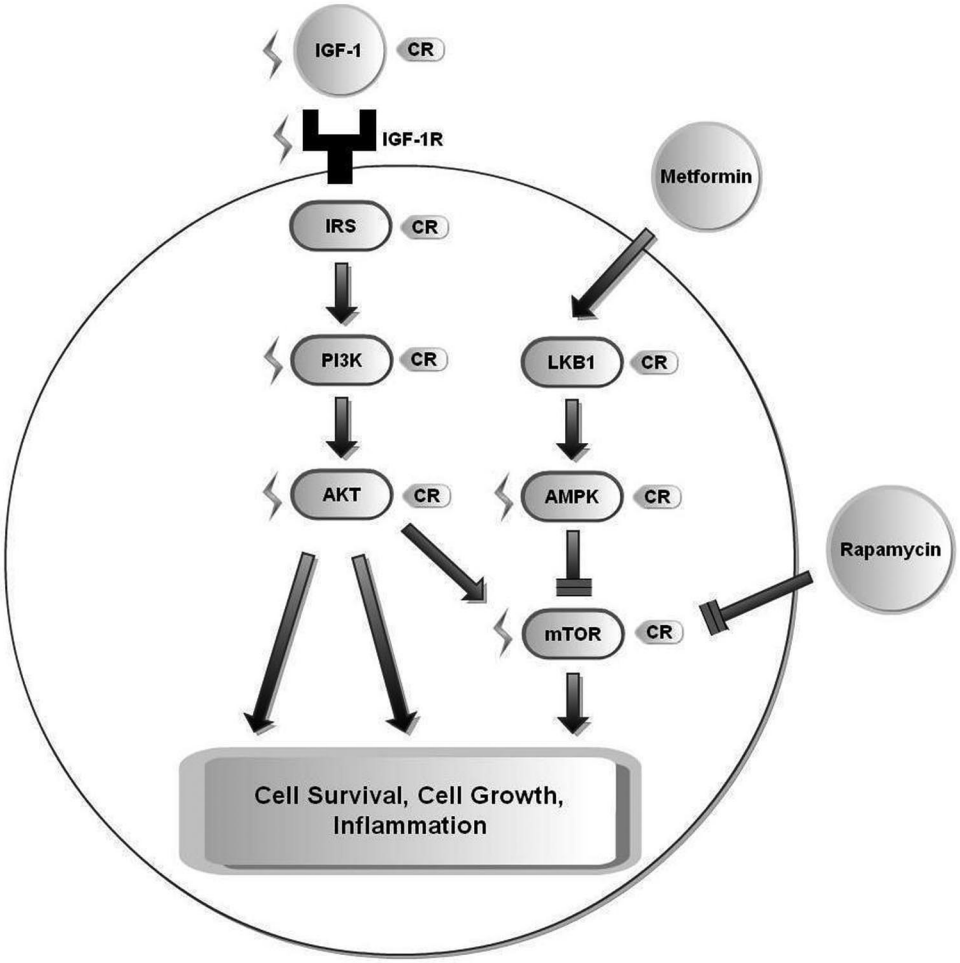

Figure 1. Molecular pathways affected by CR and irradiation. CR icon indicates pathway affected by calorie restriction. Lightening symbol indicates pathways that affect radiation sensitivity. IGF-1R, AKT, IRS, mTOR, and PI3K pathways are decreased with CR, and decrease radiation sensitivity. LKB1 and AMPK are upregulated by CR, and AMPK activation increases radiosensitivity.

Abbreviations: AMPK, AMP-activated protein kinase; CR, calorie restriction; IGF-1, insulin grown factor-1; IRS, insulin receptor substrate; LKB1, liver kinas B1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

ence include weekly meetings, frequent phone calls, cognitive–behavioral techniques [81], and newer online resources that track dietary patterns for patients who are able to be monitored directly by the physician. Cognitive–behavioral techniques have shown utility by assisting patients in identifying eating triggers and reinforcing and rewarding positive behaviors to help limit caloric consumption [82]. The Health Resource Calorie System is another method to train study participants to estimate the caloric content of food, which may also be employed in future studies.

Potential Contraindications

Although CR, especially as IF, may provide multiple benefits for patients undergoing treatment, it is not an option for all patients. Patients who are cachectic at presentation or at risk for severe weight loss may not be suitable because of the risk for further weight loss. Chronic DR may impair wound healing [83] and immune function [84], a potential issue for postoperative cancer patients as well. This issue may be mitigated by using IF based around RT, because it has been shown to result in less weight loss, especially when used for only 2–3 months [85]. Also, although many radiation and medical oncologists may approach the potential of fasting or DR in cancer patients with trepidation because of studies that linked weight loss with poor outcomes, further studies revealed this to more likely be a component of aggressive tumor biology and metabolism rather than malnutrition [86]. Regardless, cachexia occurs much less often in cancer patients than previously thought [87], and data show that breast cancer patients more often gain weight during treatment [88].

Whereas targeted therapy for several of the molecular pathways discussed above may cause serious side effects, CR through fasting in appropriate patients may actually decrease the side effects of cancer therapy. A study in which patients fasted before and after chemotherapy revealed less toxicity from treatment [89]. Patients undergoing IF have also noted less fatigue, less weakness, and fewer gastrointestinal issues [90]. Although data regarding the side effects of CR are limited, chemotherapy data have revealed that CR via IF may result in less toxicity when combined with RT as well.

Conclusions

During the last decade, the link among weight modification, dietary changes, and their influence on cancer incidence, treatment, and survival has strengthened. Based on the evidence outlined above, the benefits to overall health, weight,

CME

Table 2. Studies on the effects of CR

Tumor type	Species	Control diet	Experimental diet	Cancer-related effects vs. controls	Other effects	Year	Reference
Mammary	Mice	AL	8 CR regimens	↓ Tumor growth[b]	↑ Survival[b], ↓ body weight[b]	1914	4
None	Rats	AL	(a) 20% reduced, (b) 40% reduced, (c) varying reduction		↑ Survival[b], ↓ body weight[b]	1972	14
All tumors[a]	Mice	AL	7 CR regimens	↓ Tumors[c], ↓ mitogenesis[b,c]	↑ Survival[b], ↓ body weight[b], ↓ body temperature[b]	1983	12
Mammary	Mice	AL	40% reduced	↓ Tumor growth, ↓ *n*/size metastases, ↓ tumor angiogenesis, ↓ circulating VEGF	↓ Body weight, ↓ insulin, ↓ IGF-1	2011	8
Brain	Mice	AL	30% reduced	↓ Cell proliferation, ↓ angiogenesis, ↓ tumor vascularity, ↑ tumor apoptosis	↓ Body weight, ↓ insulin, ↓ IGF-1	2002	9
Bladder	Mice	AL	(a) 20% reduced	↑ Preneoplastic, ↑ apoptosis, ↓ tumor progression,	↓ IGF-1	1997	10
			(b) 20% reduced + IGF-1[d]	↑ cell proliferation, ↑ tumors, ↓ tumor stage	IGF normal		
All tumors[a]	p53-deficient mice	AL	(a) 40% reduced, (b) intermittent CR[e]	↓ Tumor onset time[b], ↓ survival[b]	↓ IGF-1 (only in (a)), ↓ body weight[b]	2002	11
Mammary	Rats	AL	(a) 10% reduced, (b) 20% reduced, (c) 40% reduced	↓ *n* DCIS lesions, ↓ *n* adenocarcinomas, ↓ tumor volume	↓ Body weight	1999	27
All tumors[a]	Mice	AL	25% reduced	↓ Cellular proliferation		1990	28
Liver[a]	Rats	AL	40% reduced	↓ Cellular proliferation, ↓ DNA replication, ↑ apoptosis		1994	29
Liver[a]	Mice	AL	40% reduced	↑ Apoptosis, ↓ cellular proliferation, ↓ rate of hepatoma		1994	30
Prostate	Rats	AL	30% reduced	↑ Apoptosis, ↓ tumor growth, ↓ angiogenesis, ↓ VEGF expression	↓ IGF-1	1999	91
Pancreas	Mice	AL	30% reduced	↓ Tumor size, ↓ dysplasia, ↓ proliferation, ↓ VEGF expression,	↓ Body weight ↓ IGF-1	2011	68
Mammary	Rats	AL	(a) 25% reduced, (b) 40% reduced	↓ Tumor incidence[b]	↓ Body weight[b], ↓ serum insulin[b]	1989	46
Population studies							
Breast[a]	Human	AL	Varies (anorexic patients)	↓ Tumor incidence		2004	15
All tumors[a]	Human	AL	Varies (anorexic patients)	↓ Tumor incidence		2001	16
All tumors[a]	Human	AL	Varies (gastric bypass patients)	↓ Tumor incidence		2009	17

[a]Assessed spontaneous tumor occurrence.
[b]Associated dose response.
[c]Based on time point when CR initiated.
[d]IGF-1 given.
Abbreviations: AL, ad libitum; CR, calorie restriction; DCIS, ductal carcinoma in situ; IGF-1, insulin-like growth factor 1; VEGF, vascular endothelial growth factor.

and metabolic risks, coupled with the potential therapeutic benefit of nutrient restriction by fasting, provide a compelling case for conducting clinical trials to tests the efficacy of CR and potential implementation in the care of cancer patients. Molecularly, both CR and RT have been shown to downregulate several signaling pathways that are also upregulated in cancer progression. Although CR is not currently implemented in cancer treatment strategies, studies of CR for indications other than cancer have effectively implemented CR-based diets for a period of 6 months [81].

CR by fasting is likely an effective method to potentiate the cytotoxicity of chemotherapy and RT because of the overlapping induction of molecular profiles, and it may also provide a beneficial means of improving the overall health and metabolic profiles of patients. At this time, clinical trials evaluating CR as a complementary therapy in the treatment of cancer are warranted.

Acknowledgment

This research was supported in part by the Kimmel Cancer Center's NCI Cancer Center Support Grant P30 CA56036.

Author Contributions

Conception/Design: Nicole L. Simone, Colin E. Champ, Mark V. Mishra, Lianjin Jin, Federica Sotgia, Adam P. Dicker
Provision of study material or patients: Adam P. Dicker
Collection and/or assembly of data: Nicole L. Simone, Colin E. Champ, Renato Baserga, Adam P. Dicker
Data analysis and interpretation: Nicole L. Simone, Colin E. Champ, Renato Baserga, Mark V. Mishra, Michael P. Lisanti, Richard G. Pestell, Adam P. Dicker
Manuscript writing: Nicole L. Simone, Colin E. Champ, Mark V. Mishra, Lianjin Jin, Federica Sotgia, Michael P. Lisanti, Richard G. Pestell, Adam P. Dicker
Final approval of manuscript: Nicole L. Simone, Colin E. Champ, Renato Baserga, Mark V. Mishra, Lianjin Jin, Federica Sotgia, Michael P. Lisanti, Richard G. Pestell, Adam P. Dicker

Disclosures

The authors indicated no financial relationships.

Section Editors: Suresh Senan: Lilly, Varian Medical Systems (C/A); Varian Medical Systems (H); Varian Medical Systems (H); Andrew Turrisi: None.
Reviewer "A": None
Reviewer "B": None

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

CME

References

1. Longo VD, Fontana L. Calorie restriction and cancer prevention: Metabolic and molecular mechanisms. Trends Pharmacol Sci 2010;31:89–98.

2. Hursting SD, Kari FW. The anti-carcinogenic effects of dietary restriction: Mechanisms and future directions. Mutat Res 1999;443:235–249.

3. Hursting SD, Lavigne JA, Berrigan D et al. Calorie restriction, aging, and cancer prevention: Mechanisms of action and applicability to humans. Annu Rev Med 2003;54:131–152.

4. Rous P. The influence of diet on transplanted and spontaneous mouse tumors. J Exp Med 1914; 20:433–451.

5. Rous P. The rate of tumor growth in underfed hosts. Proc Soc Exp Biol Med 1911;8:128–130.

6. Tannenbaum A. Effects of varying caloric intake upon tumor incidence and tumor growth. Ann N Y Acad Sci 1947;49:5–17.

7. Bischoff F, Long ML, Maxwell LC. Influence of caloric intake upon the growth of sarcoma. Am J Cancer 1935;180:549.

8. De Lorenzo MS, Baljinnyam E, Vatner DE et al. Caloric restriction reduces growth of mammary tumors and metastases. Carcinogenesis 2011;32: 1381–1387.

9. Mukherjee P, El-Abbadi MM, Kasperzyk JL et al. Dietary restriction reduces angiogenesis and growth in an orthotopic mouse brain tumour model. Br J Cancer 2002;86:1615–1621.

10. Dunn SE, Kari FW, French J et al. Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. Cancer Res 1997;57:4667–4672.

11. Berrigan D, Perkins SN, Haines DC et al. Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice. Carcinogenesis 2002;23:817–822.

12. Cheney KE, Liu RK, Smith GS et al. The effect of dietary restriction of varying duration on survival, tumor patterns, immune function, and body temperature in B10C3F1 female mice. J Gerontol 1983; 38:420–430.

13. Ross MH, Bras G. Lasting influence of early caloric restriction on prevalence of neoplasms in the rat. J Natl Cancer Inst 1971;47:1095–1113.

14. Nolen GA. Effect of various restricted dietary regimens on the growth, health and longevity of albino rats. J Nutr 1972;102:1477–1493.

15. Michels KB, Ekbom A. Caloric restriction and incidence of breast cancer. JAMA 2004;291:1226–1230.

16. Mellemkjaer L, Emborg C, Gridley G et al. Anorexia nervosa and cancer risk. Cancer Causes Control 2001;12:173–177.

17. Adams TD, Stroup AM, Gress RE et al. Cancer incidence and mortality after gastric bypass surgery. Obesity (Silver Spring) 2009;17:796–802.

18. Brolin RL, Robertson LB, Kenler HA et al. Weight loss and dietary intake after vertical banded gastroplasty and Roux-en-Y gastric bypass. Ann Surg 1994;220:782–790.

19. Dias MC, Ribeiro AG, Scabim VM et al. Dietary intake of female bariatric patients after anti-obesity gastroplasty. Clinics (Sao Paulo) 2006;61:93–98.

20. Trostler N, Mann A, Zilberbush N et al. Weight loss and food intake 18 months following vertical banded gastroplasty or gastric bypass for severe obesity. Obes Surg 1995;5:39–51.

21. Kagawa Y. Impact of Westernization on the nutrition of Japanese: Changes in physique, cancer, longevity and centenarians. Prev Med 1978;7:205–217.

22. Hite AH, Berkowitz VG, Berkowitz K. Low-carbohydrate diet review: Shifting the paradigm. Nutr Clin Pract 2011;26:300–308.

23. Calle EE, Rodriguez C, Walker-Thurmond K et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638.

24. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–846.

25. Kroenke CH, Chen WY, Rosner B et al. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 2005;23:1370–1378.

26. Ligibel J. Obesity and breast cancer. Oncology (Williston Park) 2011;25:994–1000.

27. Zhu Z, Jiang W, Thompson HJ. Effect of energy restriction on tissue size regulation during chemically induced mammary carcinogenesis. Carcinogenesis 1999;20:1721–1726.

28. Lok E, Scott FW, Mongeau R et al. Calorie restriction and cellular proliferation in various tissues of the female Swiss Webster mouse. Cancer Lett 1990;51:67–73.

29. Grasl-Kraupp B, Bursch W, Ruttkay-Nedecky B et al. Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. Proc Natl Acad Sci U S A 1994;91:9995–9999.

30. James SJ, Muskhelishvili L. Rates of apoptosis and proliferation vary with caloric intake and may influence incidence of spontaneous hepatoma in C57BL/6 x C3H F1 mice. Cancer Res 1994;54:5508–5510.

31. Raffaghello L, Lee C, Safdie FM et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci U S A 2008;105: 8215–8220.

32. Macaulay VM. Insulin-like growth factors and cancer. Br J Cancer 1992;65:311–320.

33. Yuen JS, Macaulay VM. Targeting the type 1 insulin-like growth factor receptor as a treatment for cancer. Expert Opin Ther Targets 2008;12:589–603.

34. Creighton CJ, Casa A, Lazard Z et al. Insulin-like growth factor-I activates gene transcription programs strongly associated with poor breast cancer prognosis. J Clin Oncol 2008;26:4078–4085.

35. Taunk NK, Goyal S, Moran MS et al. Prognostic significance of IGF-1R expression in patients treated with breast-conserving surgery and radiation therapy. Radiother Oncol 2010;96:204–208.

36. Resnicoff M, Coppola D, Sell C et al. Growth inhibition of human melanoma cells in nude mice by antisense strategies to the type 1 insulin-like growth factor receptor. Cancer Res 1994;54:4848–4850.

37. Papa V, Pezzino V, Costantino A et al. Elevated insulin receptor content in human breast cancer. J Clin Invest 1990;86:1503–1510.

38. Peyrat JP, Bonneterre J, Hecquet B et al. Plasma insulin-like growth factor-1 (IGF-1) concentrations in human breast cancer. Eur J Cancer 1993; 29A:492–497.

39. Baserga R. The contradictions of the insulin-like growth factor 1 receptor. Oncogene 2000;19: 5574–5581.

40. Rubin R, Baserga R. Insulin-like growth factor-I receptor. Its role in cell proliferation, apoptosis, and tumorigenicity. Lab Invest 1995;73:311–331.

41. Bonneterre J, Peyrat JP, Beuscart R et al. Prognostic significance of insulin-like growth factor 1 receptors in human breast cancer. Cancer Res 1990; 50:6931–6935.

42. Adélaïde J, Finetti P, Bekhouche I et al. Integrated profiling of basal and luminal breast cancers. Cancer Res 2007;67:11565–11575.

43. Turner BC, Haffty BG, Narayanan L et al. Insulin-like growth factor-I receptor overexpression mediates cellular radioresistance and local breast cancer recurrence after lumpectomy and radiation. Cancer Res 1997;57:3079–3083.

44. Railo MJ, von Smitten K, Pekonen F. The prognostic value of insulin-like growth factor-I in breast cancer patients. Results of a follow-up study on 126 patients. Eur J Cancer 1994;30A:307–311.

45. Perer ES, Madan AK, Shurin A et al. Insulin-like growth factor I receptor antagonism augments response to chemoradiation therapy in colon cancer cells. J Surg Res 2000;94:1–5.

46. Ruggeri BA, Klurfeld DM, Kritchevsky D et al. Caloric restriction and 7,12-dimethylbenz(a)anthracene-induced mammary tumor growth in rats: Alterations in circulating insulin, insulin-like growth factors I and II, and epidermal growth factor. Cancer Res 1989;49:4130–4134.

47. Muñoz MT, Argente J. Anorexia nervosa in female adolescents: Endocrine and bone mineral density disturbances. Eur J Endocrinol Sep 2002; 147:275–286.

48. Dunn SE, Hardman RA, Kari FW et al. Insulin-like growth factor 1 (IGF-1) alters drug sensitivity of HBL100 human breast cancer cells by inhibition of apoptosis induced by diverse anticancer drugs. Cancer Res 1997;57:2687–2693.

49. Cosaceanu D, Budiu RA, Carapancea M et al. Ionizing radiation activates IGF-1R triggering a cytoprotective signaling by interfering with Ku-DNA binding and by modulating Ku86 expression via a p38 kinase-dependent mechanism. Oncogene 2007;26:2423–2434.

50. Wen B, Deutsch E, Marangoni E et al. Tyrphostin AG 1024 modulates radiosensitivity in human breast cancer cells. Br J Cancer 2001;85:2017–2021.

51. Lee C, Safdie FM, Raffaghello L et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. Cancer Res 2010;70:1564–1572.

52. Clemmons DR, Underwood LE. Nutritional regulation of IGF-I and IGF binding proteins. Ann Rev Nutr 1991;11:393–412.

53. Barger JL, Kayo T, Vann JM et al. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. PLoS One 2008;3:e2264.

54. Baserga R. The insulin receptor substrate-1: A biomarker for cancer? Exp Cell Res 2009;315:727–732.

55. Fresno Vara JA, Casado E, de Castro J et al.

CME

PI3K/Akt signalling pathway and cancer. Cancer Treat Rev 2004;30:193–204.

56. Guppy A, Jamal-Hanjani M, Pickering L. Anticancer effects of metformin and its potential use as a therapeutic agent for breast cancer. Future Oncol 2011;7:727–736.

57. Ouyang P, Jiang Y, Doan HM et al. Weight loss via exercise with controlled dietary intake may affect phospholipid profile for cancer prevention in murine skin tissues. Cancer Prev Res (Phila) 2010;3: 466–477.

58. Kandel ES, Skeen J, Majewski N et al. Activation of Akt/protein kinase B overcomes a G(2)/m cell cycle checkpoint induced by DNA damage. Mol Cell Biol 2002;22:7831–7841.

59. Price BD, Youmell MB. The phosphatidylinositol 3-kinase inhibitor wortmannin sensitizes murine fibroblasts and human tumor cells to radiation and blocks induction of p53 following DNA damage. Cancer Res 1996;56:246–250.

60. Söderlund K, Pérez-Tenorio G, Stal O. Activation of the phosphatidylinositol 3-kinase/Akt pathway prevents radiation-induced apoptosis in breast cancer cells. Int J Oncol 2005;26:25–32.

61. Cataldi A, Zauli G, Di Pietro R et al. Involvement of the pathway phosphatidylinositol-3-kinase/AKT-1 in the establishment of the survival response to ionizing radiation. Cell Signal 2001;13:369–375.

62. Gupta AK, Cerniglia GJ, Mick R et al. Radiation sensitization of human cancer cells in vivo by inhibiting the activity of PI3K using LY294002. Int J Radiat Oncol Biol Phys 2003;56:846–853.

63. Jiang W, Zhu Z, Thompson HJ. Dietary energy restriction modulates the activity of AMP-activated protein kinase, Akt, and mammalian target of rapamycin in mammary carcinomas, mammary gland, and liver. Cancer Res 2008;68:5492–5499.

64. Lin K, Hsin H, Libina N et al. Regulation of the *Caenorhabditis elegans* longevity protein DAF-16 by insulin/IGF-1 and germline signaling. Nat Genet 2001;28:139–145.

65. Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature 2006; 441:424–430.

66. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell 2006;124: 471–484.

67. Moore T, Beltran L, Carbajal S et al. Dietary energy balance modulates signaling through the Akt/mammalian target of rapamycin pathways in multiple epithelial tissues. Cancer Prev Res (Phila) 2008;1:65–76.

68. Lashinger LM, Malone LM, Brown GW et al. Rapamycin partially mimics the anticancer effects of calorie restriction in a murine model of pancreatic cancer. Cancer Prev Res (Phila) 2011;4:1041–1051.

69. Shackelford DB, Shaw RJ. The LKB1-AMPK pathway: Metabolism and growth control in tumour suppression. Nat Rev Cancer 2009;9:563–575.

70. Steinberg GR, Kemp BE. AMPK in health and disease. Physiol Rev 2009;89:1025–1078.

71. Zannella VE, Cojocari D, Hilgendorf S et al. AMPK regulates metabolism and survival in response to ionizing radiation. Radiother Oncol 2011; 99:293–299.

72. He Q, Gao Z, Yin J et al. Regulation of HIF-1α activity in adipose tissue by obesity-associated factors: Adipogenesis, insulin, and hypoxia. Am J Physiol Endocrinol Metab 2011;300:E877–E885.

73. Mazzoletti M, Bortolin F, Brunelli L et al. Combination of PI3K/mTOR inhibitors: Antitumor activity and molecular correlates. Cancer Res 2011;71: 4573–4584.

74. Shaw LM. The insulin receptor substrate (IRS) proteins: At the intersection of metabolism and cancer. Cell Cycle 2011;10:1750–1756.

75. Sanli T, Rashid A, Liu C et al. Ionizing radiation activates AMP-activated kinase (AMPK): A target for radiosensitization of human cancer cells. Int J Radiat Oncol Biol Phys 2010;78:221–229.

76. Slichenmyer WJ, Nelson WG, Slebos RJ et al. Loss of a p53-associated G1 checkpoint does not decrease cell survival following DNA damage. Cancer Res 1993;53:4164–4168.

77. Green AS, Chapuis N, Maciel TT et al. The LKB1/AMPK signaling pathway has tumor suppressor activity in acute myeloid leukemia through the repression of mTOR-dependent oncogenic mRNA translation. Blood 2010;116:4262–4273.

78. Goodwin PJ, Stambolic V, Lemieux J et al. Evaluation of metformin in early breast cancer: A modification of the traditional paradigm for clinical testing of anti-cancer agents. Breast Cancer Res Treat 2011;126:215–220.

79. Kalm LM, Semba RD. They starved so that others be better fed: Remembering Ancel Keys and the Minnesota experiment. J Nutr 2005;135:1347–1352.

80. Kelley DE, Wing R, Buonocore C et al. Relative effects of calorie restriction and weight loss in non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1993;77:1287–1293.

81. Heilbronn LK, de Jonge L, Frisard MI et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: A randomized controlled trial. JAMA 2006;295:1539–1548.

82. Foster GD, Makris AP, Bailer BA. Behavioral treatment of obesity. Am J Clin Nutr 2005;82:230S–235S.

83. Reed MJ, Penn PE, Li Y et al. Enhanced cell proliferation and biosynthesis mediate improved wound repair in refed, caloric-restricted mice. Mech Ageing Dev 1996;89:21–43.

84. Fontana L, Partridge L, Longo VD. Extending healthy life span—from Yeast to humans. Science 2010;328:321–326.

85. Lee C, Raffaghello L, Brandhorst S et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Sci Transl Med 2012;4:124ra127.

86. Evans WK, Nixon DW, Daly JM. A randomized study of oral nutritional support versus ad lib nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. J Clin Oncol 1987;5:113–124.

87. Fox KM, Brooks JM, Gandra SR et al. Estimation of Cachexia among Cancer Patients Based on Four Definitions. J Oncol 2009;2009:693458.

88. Demark-Wahnefried W, Rimer BK, Winer EP. Weight gain in women diagnosed with breast cancer. J Am Diet Assoc 1997;97:519–526, 529; quiz 527–528.

89. Safdie FM, Dorff T, Quinn D et al. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY) 2009;1:988–1007.

90. Raffaghello L, Safdie F, Bianchi G et al. Fasting and differential chemotherapy protection in patients. Cell Cycle 2010;9:4474–4476.

91. Mukherjee P, Sotnikov AV, Mangian HJ, et al. Energy intake and prostate tumor growth, angiogenesis, and vascular endothelial growth factor expression. J Natl Cancer Inst 1999;91:512–523.